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Absorption, distribution, metabolism, and excretion of the cutaneous penetration enhancer Azone

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

1989

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wiechers, J. W. (1989). *Absorption, distribution, metabolism, and excretion of the cutaneous penetration enhancer Azone*. s.n.

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SUMMARY

Azone® (1-dodecylazacycloheptan-2-one; Nelson Research, Irvine, CA, USA) has been shown to be of great value in enhancing the flux of drugs through both animal and human skin *in-vitro*. This property opens new possibilities for dermal and transdermal drug delivery of compounds that are normally absorbed by the skin in insufficient amounts. However, prior to human use in daily clinical practice, adequate information is required concerning the fate of Azone in the body. This thesis describes the absorption, distribution, metabolism, and elimination of this penetration enhancer.

A twofold approach was chosen. On the one hand, clinical studies were performed in which radioactive Azone was applied to the forearm of volunteers. The absorption, distribution in the skin, and excretion of Azone and Azone-derived material were studied, in combination with the compound's metabolic profile in the major excretion media. On the other hand, metabolic studies in various animal species, isolated livers and in (sub)cellular liver fractions were performed and compared to the human *in-vivo* metabolism.

Prior to the presentation of the experimental results, detailed background information is provided on the skin as a barrier in relation to percutaneous absorption of drugs (Chapter 2). Subsequently, the reader is familiarized with Azone's pharmaceutical and analytical aspects (Chapter 3).

Chapters 4 and 5 describe the percutaneous absorption of Azone when dosed as the neat liquid, its skin distribution, and disposition in the excreta. ^{14}C -Azone, labelled in the α -position in the side-chain, was dosed as no method was available to follow the unlabelled compound. It could be demonstrated that the percutaneous absorption of the compound was very low: Less than 0.5% either after a single dose for 4 h under non-occlusive conditions, or a single dose for 12 h under occlusive conditions. Accumulation of Azone in the stratum corneum did not occur. Elimination of radioactivity was complete within 120 h and took place predominantly (>95%) through the urine. Metabolic profiling of the latter revealed virtually complete extensive metabolism of Azone to at least three very polar metabolites.

The percutaneous absorption of ^{14}C -Azone, incorporated in a therapeutic formulation at a concentration of 1.6%, also containing propylene glycol and the therapeutic agent triamcinolone acetonide (0.05%), was studied following multiple dermal application under occlusive conditions (Chapter 6). Absorption of Azone was found to be higher at 3.5%, but the absolute amounts were approximately the same as seen in the single dose study under occlusive conditions, indicating that the flux of Azone through human skin is even lower when dosed in a therapeutic formulation. Absorption plateaued within 3 days. Higher levels of radioactivity could be retrieved in the stratum corneum following multiple dosing when compared to single dosing, but again, there were no indications of accumulation in the skin. All other kinetic parameters were not affected by the therapeutic formulation.

Chapter 7 describes a new method to establish cutaneous metabolism of topically applied drugs, making use of the outward migration of substances through the skin. ^{14}C -Azone-derived radioactivity appeared to be present in the stratum corneum as the unchanged compound only. Yet, Cyoctol, another compound that is being tested for dermal application,

showed considerable cutaneous metabolism.

Chapters 8 and 9 describe the metabolic studies performed in animal species, isolated liver, and (sub)cellular liver material. Azone appeared to be metabolized to different compounds in hamster, rat, monkey, and man, the polarity of the bulk of their respective metabolites increasing in this order. In all species, the excretion was mainly by the kidneys. As rat metabolites most closely corresponded the human biotransformation products, this animal was selected for additional *in-vivo* and *in-vitro* studies. It could be demonstrated that the transposition of the radioactive isotope from the side-chain to the ring did not affect the metabolic profiles, suggesting that total cleavage of the side-chain or ring-opening with subsequent removal of the carboxyl functions did not take place. Likewise, intravenous and oral administration of Azone resulted in the same metabolic profile, suggesting the gastro-intestinal tract to be not involved in the metabolism of Azone. Subsequently, both rat liver perfusion and rat hepatocyte experiments demonstrated this organ to be capable of bioconverting Azone to the same metabolites as encountered in the *in-vivo* profile, via the formation of transient, relative non-polar metabolites that were also produced by the human hepatocytes. Rat and human microsomes were also capable of producing these non-polar metabolites but failed to generate the *in-vivo* products of either species.

Chapter 10 describes the influence of Azone on the percutaneous absorption of triamcinolone acetonide and provides the first evidence that Azone acts as a penetration enhancer *in-vivo* in human skin when dosed in a therapeutic formulation. Enhancement factors were introduced to quantitate the influence of Azone. The enhancement factor was found to be 3.2 for single dosing of Azone, whereas multiple dosing further increased the extent of absorption by a factor 2.1, resulting in a total enhancement factor of 6.8.

The results presented in this thesis indicate that due to its low percutaneous absorption, the body burden of Azone is low. Accumulation does not take place in the skin, nor at any other site of the body. Excretion is complete, rapid (within 3-5 days), and predominantly into the urine in which it is present as polar metabolites. These combined results suggest Azone to be safe for human use.